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Near Infrared Spectroscopy for Improving Breast Core Needle Biopsy

(Annual Report : 09/01/2004 – 08/31/2005)

Carmalyn Lubawy, Principal Investigator

Note: Carmalyn Lubawy left the University of Wisconsin on July 1, 2005. These results only reflect progress made on this project prior to her departure.

1. Introduction

Currently one million needle biopsies are performed in the United States, annually, for the diagnosis of breast cancer [1]. However, repeat biopsies are experienced by 7% of patients [1, 2].

Near infrared (NIR) optical spectroscopy has the potential to improve the accuracy of image guided core needle biopsy by providing a non-destructive diagnosis of the tissue before it is removed. In this technique photon density waves are launched into the tissue and collected some distance away from the source [3]. A number of groups have demonstrated NIR diffuse optical spectroscopy and imaging can be exploited for the non-invasive detection of breast cancer in the intact breast [3-6].

The introduction of the large diameter Mammatome biopsy needle allows NIR spectroscopy to be performed directly on the breast tissue of interest, as it is large enough to allow the insertion of a fiber optic probe. Thus NIR spectroscopy may directly augment a clinical procedure already widely used throughout the United States.

2. Body

The tasks from the approved statement of work are listed for reference and are followed by the progress made on each task.

Task 1: Assemble near infrared spectroscopy instrument (months 1-9)

- a. Identify and acquire needed parts for instrument
- b. Assemble parts into instrument using best practices
- c. Measure noise, drift, dynamic range, and phase accuracy.
- d. Consult books and Burk O'Neal on improving parameters measured in c.
- e. Make modifications, until parameters are within required limits.

Successful completion of this task will be an instrument with noise floor at least 5 times lower than the expected signal level, and fully characterized drift, dynamic range, and phase accuracy.

This phase has been completed, and noise floor and drift have been characterized. The instrument consists of a laser diode driver, a network analyzer, three laser diodes (811nm, 849, and 660nm), an optical switch, an avalanche photo diode (APD), and a 19dB amplifier. The average power delivered at the probe tip was approximately 6 mW. The instrument is configured so each measurement consists of 101 data points over the frequency range of 50-150MHz at each wavelength. At a bandwidth of 15 Hz (resulting in a measurement sweep time of 8 seconds), the signal to noise ratio of the instrument and probe was greater than 300:1 over the measurement range in a representative liquid phantom. Amplitude drift is less than $\pm 1.5\%$ and phase drift is less than $\pm 2\%$. Dynamic range and phase accuracy were not characterized because of difficulty in setting up these tests. Because these test were for characterization only, it was deemed that the time required to set up the tests was not worth the information gleaned from them.

Task 2: Design and construction of probe. (months 1 – 9)

- a. Identify optical construction of probe
- b. Perform throughput analysis
- c. Design mechanical construction of probe
- d. Construct probe
- e. Characterize throughput of probe

Successful completion of this task will be a characterized probe that possesses the throughput and mechanical attributes necessary for it to be utilized with the Mamatome core biopsy needle and the instrument built in task 1.

This task was modified slightly. The probe was designed to possess the mechanical attributes necessary to be utilized in the Suros Biopsy needle. This was done because the 3cm bend radius requirement for use with the Mamatome needle proved to be too challenging, and a probe used with the Suros needle has no bend radius requirements. Details of the probe construction can be found in the attached paper which was published in Optics Letters.

Task 3: Homogeneous phantoms. (months 10-16)

- a. Build solid phantom and verify optical properties.
- b. Develop calibration routine
- c. Test probe, instrument, calibration routine, and inverse algorithm on a series of homogenous phantoms.
- d. Extract optical properties
- e. Make iterative adjustments to the instrument's sweep time, number of frequencies measured, and number of measurements averaged, as well as to the calibration routine, optical coupling to calibration phantom, and the extraction algorithm.
- f. Perform measurements with probe inserted into the needle
- g. Extract optical properties.
- h. Verify the needle did not change system.

Successful completion of this task will be the correct retrieve of the optical properties for a series of homogeneous phantoms in the range of the normal to diseased tissue.

Results of the solid phantom study can be found in the attached paper which was published in Optics Letters. The calibration routine has been developed. It was discovered that most of the probes that have been built must be calibrated every time they are used to recover optical properties. The instruments configuration and sweep time were not optimized due to time requirements. It was found that the measurement results were very different when the probe was inside the needle and when it was used without the needle, so the calibration procedure states that the probe must be in the same environment (with or without a needle) when calibrated as it is in intended use.

Task 4: Tissue samples (months 17-18)

- a. Submit form for tissue collection (month 12)
- b. Move instrument and probe to hospital.
- c. Perform verification check on instrument and probe.
- b. Perform measurements on 5 breast tissue samples.
- d. Use algorithm to retrieve optical properties

Successful completion of this task will be retrieval of reasonable optical properties from samples.

This step was not completed because of logistical problems in getting and testing samples and limited information that would be gleaned from this experiment. In its place a study was completed on heterogeneous phantoms that were representative of diseased tissue surrounded by normal breast tissue. The results of this study can be seen in the attached paper published in Optics Letters.

Task 5: Preparation for clinical studies (month 18)

- Work with Dr. Burnside on exact probe procedures.
- Work with Dr. Burnside and Histologist on method to track samples' original orientation, and the order they were removed.
- Work with histologist on what and how information will be reported to us.

Successful completion of this task will be a procedure, which Dr. Burnside, the histologist, and myself are confident that it will go smoothly in the clinic and will provide the necessary information for this study.

This step has been completed.

Task 6: Pilot study 5 women (months 19-20)

- Perform measurements in *in vivo* of 5 women undergoing core needle biopsy.
- Retrieve optical properties from each measurement.
- Calculate oxygenated and deoxygenated hemoglobin concentrations from the optical properties
- After each trial review data and procedure, and make any necessary adjustments

Successful completion of this task will be verification that this system and will perform in a clinical setting, and that there is a procedure which can be used consistently, will go smoothly in the clinic and will provide the necessary information for this study.

This part of the study has been completed. Of the 6 measurements made on each volunteer, a limited number resulted in usable data. Some causes for data being thrown out include laser diode malfunction, aperture in needle not being open, drift in system, and calculated hemoglobin concentrations being outside of reasonable range. We believe that the drift in the system is due to changes in tissue such as bleeding, lidocaine push draining out of cavity, and needle rotation during measurement. The reasonable results from 4 of first volunteers can be seen in figures 1 and 2.

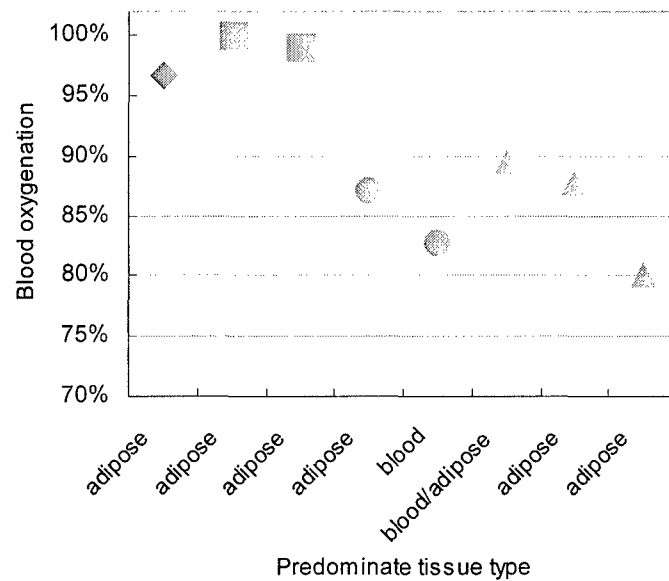


Figure 1: Blood oxygenation of tissue removed during a biopsy. Each point represents a different sample. Each different shape represents a different volunteer.

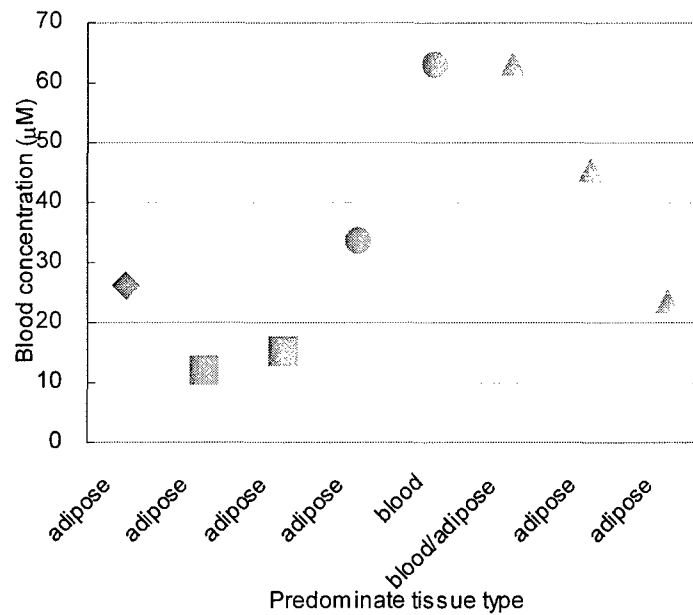


Figure 2: Blood oxygenation of tissue removed during a biopsy. Each point represents a different sample. Each different shape represents a different volunteer.

- Task 7: *in vivo* study (months 21 – 31)
- Perform measurements *in vivo* of 25 women undergoing core needle biopsy.
 - Retrieve optical properties.
 - Calculate oxygenated and deoxygenated hemoglobin concentrations from the optical properties

Successful completion of this task will be optical and biological properties which can be used to differentiate malignant from non-malignant tissue types.

This part of the study has not yet been completed and will be completed by a new student taking over the project.

- Task 8: Analyze data (months 22 – 36)
- a. Consolidate optical and physiological measures into a few parameters.
 - b. Eliminate features that do not have statistically significant differences between malignant and non-malignant tissue types.
 - c. Eliminate features that are correlated with age and menopausal status.
 - d. Use Support Vector Machine to classify samples
 - e. Cross validate training of Support Vector Machine
- Successful completion of this task will be an algorithm, which can discriminate between malignant and non-malignant tissue.

This part of the study has not yet been completed and will be completed by a new student taking over the project.

3. Key Research finding:

It is possible to measure the hemoglobin concentration and saturation of human breast tissue from inside a core biopsy needle using near infrared optical spectroscopy.

4. Reportable outcomes:

The outcomes of this study are that it is feasible to measure NIR photon migration signals during core needle biopsy of the breast. This has been achievable by building a customized fiber-optic probe for use in the Suros core needle biopsy probe. The probe has been characterized in extensive phantom studies. However, more clinical data is needed to prove the diagnostic value of this technology. This will be carried out by a future student working on this project.

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Endoscopically compatible near-infrared photon migration probe

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We have developed a 2.3-mm-diameter fiber-optic probe for near-infrared photon migration spectroscopy that can be inserted into the body through an endoscope or biopsy needle. This probe is specifically designed to be inserted into a core biopsy needle to facilitate optical sampling of lesions during breast needle biopsy. This probe was tested on tissue phantoms containing heterogeneities (to stimulate breast lesions) of various sizes and optical properties. Under the conditions tested, the probe can measure the absorption coefficient to within 30% for heterogeneities with radii as small as 10 mm. © 2004 Optical Society of America

OCIS codes: 170.4580, 170.5280, 170.6510.

Photon migration spectroscopy (PMS) is a technique in which near-infrared photon density waves are launched into a medium and are collected as much as several centimeters away from the source, permitting measurement of scattering and absorption several centimeters below the source–detector plane.¹ PMS has been used to monitor and image brain and muscle oxygenation¹ and to noninvasively detect changes in hemoglobin oxygenation, vascularity, and water content of breast cancer² by use of optical fibers placed perpendicular to the skin directly above the region of interest.^{1,2}

PMS probes placed on the skin have a maximum measurement depth of several centimeters, and the measurement is an average of the optical properties of the tissue that the light traverses. Thus the accuracy of transcutaneous PMS is limited if the region of interest is only a portion of the optically sampled tissue volume, and this approach does not provide access to deeply embedded tissues. A small-diameter PMS probe could be used with endoscopes or biopsy needles to more accurately measure the optical properties of regions of interest in deeply embedded organs such as the prostate or the liver or within large tissue volumes such as the breast.

Currently, one million needle biopsies of the breast are performed in the United States annually.³ Needle biopsies remove only a small amount of tissue, yielding a false-negative rate of as much as 8% (Ref. 4) and thus necessitating repeat biopsies in as many as 7% of patients.^{3,5} PMS has the potential to rapidly and nondestructively diagnose the tissue at the tip of the biopsy needle as normal, benign, or cancerous. Thus it can augment an x-ray or ultrasound guided breast needle biopsy by determining if the needle is in the correct position, thus increasing the likelihood that abnormal tissue is sampled. This property should reduce the false-negative rate and the number of women who must endure a repeat biopsy.

Our fiber-optic probe is designed to be inserted into the 2.7-mm-diameter bore of a Mammotome breast biopsy needle (Ethicon Endo Surgery). The needle has a solid tip and a 16-mm-long, 2.5-mm-wide aperture along its side that is used for tissue collection and

PMS measurements. Figure 1 is a conceptual picture of the tip of the fiber-optic probe inside the biopsy needle. Overall, the probe consists of side-firing fiber tips encased in a rigid optical quartz cap through which light may be transmitted. These fibers are relayed to the PMS instrument via flexible tubing, which is connected to the cap. This PMS probe was designed by our group and fabricated by Polymicro Technologies.

The first design consideration for this probe was that it will be in contact with the inside of the human body. Thus all materials used in the probe tip (an optical quartz cap, flexible Tygon tubing, and a proprietary epoxy), comply with U.S. Pharmacopoeia class VI standards.

The Mammotome device does not provide straight-line access to the bore of the needle. Geometric calculations have shown that the probe needs to have an effective bend radius of 3 cm or less for insertion into the needle. The two primary factors that affect the bend radius are the length of the quartz cap and the diameter (stiffness) of the largest optical fiber used in the probe. The mean penetration depth of the collected light increases with increasing source–detector separation (SDS), and the SDS determines the minimum length of the cap. Thus the SDS and the fiber diameters were selected to maximize the sampling depth and the throughput, respectively, while an effective bend radius of 3 cm

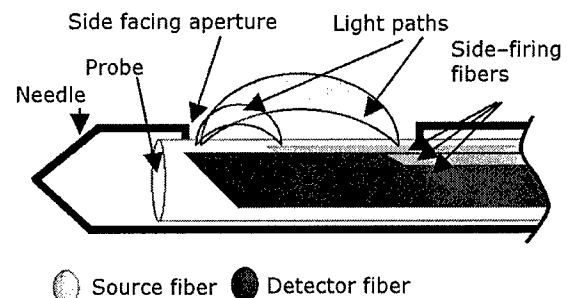


Fig. 1. Conceptual picture of the fiber-optic probe inside the biopsy needle, with the light paths extending into the tissue through the aperture.

was maintained. The resultant probe specifications are as follows: two source fibers with a core diameter of 200 μm and a numerical aperture of 0.22, a detector fiber with a core diameter of 600 μm and a numerical aperture of 0.22, an optical quartz cap with a length of 15 mm and an outer diameter of 2.4 mm, and a maximum SDS of 10 mm (the extra cap length seals the tip and joins the cap to the Tygon tube). A second source fiber was incorporated at a SDS of 5 mm. All fibers were polished at an angle of 43° and radially oriented such that the light from each fiber was normal to the circumference of the quartz cap, minimizing specular reflection into the detector fiber. We fixed the relative placement and orientation of the fiber tips by gluing the fibers together. Epoxy at the junction of the rigid cap and the Tygon tube fixed the fibers inside the cap. The outer diameter of the cap was stepped down such that it fit inside the Tygon tube to provide strength at the junction and to make the junction smooth for easy insertion and removal of the probe. The rest of the probe was fabricated by standard construction techniques. Figure 2 shows a top-down photograph of the tip of the probe.

The instrument to which the probe is coupled is a frequency-domain system that is similar in design to one described in the literature.⁶ It consists of a laser diode driver, a network analyzer, three laser diodes (811, 849, and 905 nm), an optical switch, an avalanche photodiode, and a 19-dB amplifier. The 811-nm laser was used for the experiments presented in this Letter. The average power delivered at the probe tip was approximately 6 mW. For each measurement, 101 data points were collected over the frequency range 50–150 MHz. At a bandwidth of 15 Hz (resulting in a measurement sweep time of 8 s), the signal-to-noise ratio of the instrument and the probe was greater than 300:1 over the measurement range in a representative liquid phantom. This instrument records phase and amplitude data at both SDSs. These data were fitted to a diffusion equation for an infinite medium. For homogenous media the multifrequency, two-SDS method and the multifrequency single-SDS method provide similar results, but the two-SDS method was used in subsequent analyses because it obviated the need for calibration phantoms.⁶

First, the accuracy of the probe for measuring the optical properties of semisolids that are representative of normal and diseased tissue was characterized.^{1,2} Agar tissue phantoms with a reduced scattering coefficient (μ_s') of 10 cm^{-1} and absorption coefficients (μ_a) that ranged from 0.02 to 0.20 cm^{-1} were constructed with Intralipid (scatterer) and India ink (absorber).⁷

Figure 3 shows the measured μ_a as a function of the theoretical μ_a of the homogeneous phantom. It can be seen that the retrieved μ_a is very accurate from 0.02 to 0.15 cm^{-1} . At a value of μ_a of 0.20 cm^{-1} there is some roll-off. We believe that this roll-off is caused by light leaking directly from the source to the detector fiber without exiting the probe, swamping the signal detected from the darker phantoms. The measured μ_s' was within 30% of theoretical with no discernable trend with varying absorption coefficients.

Next, semisolid tissue phantoms that simulate breast tissue with a lesion were created. Figure 4 shows a drawing of the test setup. Phantoms made from agar, Intralipid, and ink were constructed with cylindrical heterogeneities that were approximately as tall as they were wide. The background phantom was representative of normal breast tissue with values of μ_a and μ_s' of 0.05 and 10 cm^{-1} , respectively.¹ The cylindrical heterogeneities had optical properties representative of malignant breast tissue with μ_a values of 0.10, 0.15, and 0.20 cm^{-1} and a constant μ_s' of 10 cm^{-1} .^{1,2} The probe tip was approximately at the bottom of the heterogeneity.

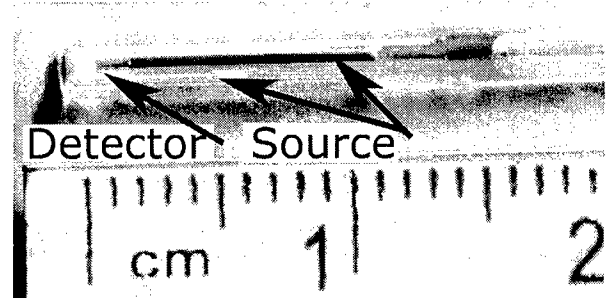


Fig. 2. Photograph of the tip of the PMS probe. There are three side-firing fibers (two source and one detector fiber) fixed inside a quartz cap, which is connected to flexible Tygon tubing.

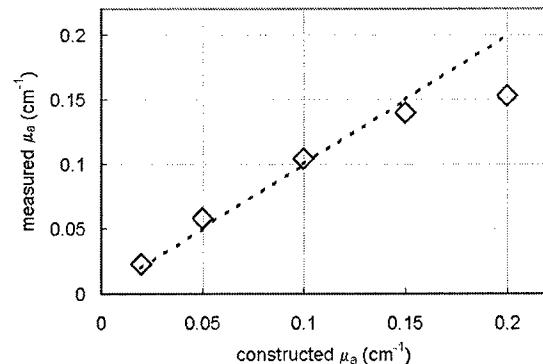


Fig. 3. The measured (diamonds) and theoretical (dashed line) absorption coefficient (μ_a) of the homogeneous agar phantoms for μ_a from 0.02 to 0.20 cm^{-1} and for a value of μ_s' of 10 cm^{-1} .

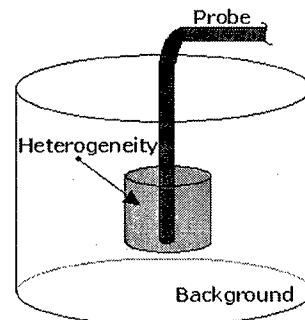


Fig. 4. Test setup in which the probe was used to make PMS measurements of synthetic tissue phantoms that simulate breast tissue with lesions.

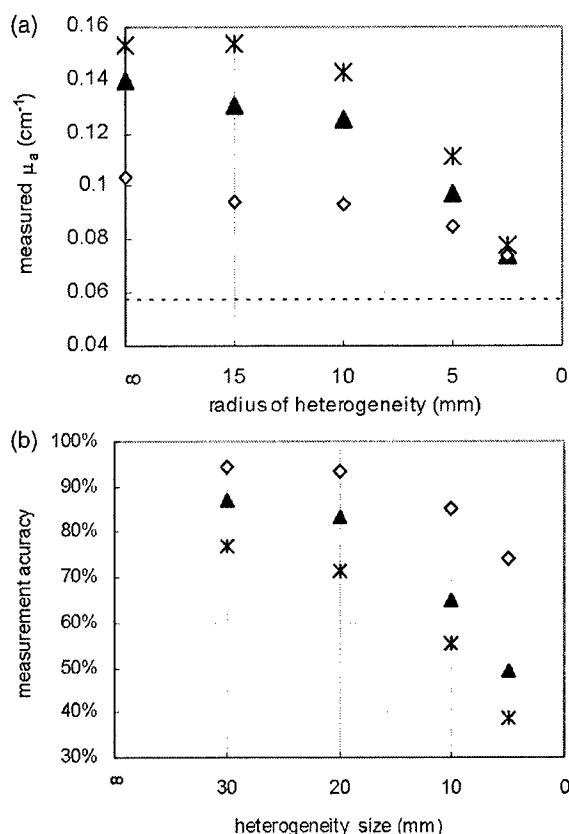


Fig. 5. (a) Measured absorption coefficient (μ_a) of a tissue phantom containing a heterogeneity and (b) measurement accuracy for data presented in (a). The values of μ_a of the heterogeneities are (*) 0.20 cm^{-1} , (▲) 0.15 cm^{-1} , and (◇) 0.10 cm^{-1} . The dashed line in (a) represents the measured μ_a of the background. The reduced scattering coefficient (μ_s') of the entire phantom is 10 cm^{-1} .

Figure 5 shows the measured absorption coefficients for heterogeneities of various sizes and absorption coefficients, and the accuracy of these measurements. As expected, the measured absorption coefficient is closest to that of the heterogeneity when the heterogeneity comes closer to filling the optical sampling volume. As the size of the heterogeneity decreases, more of the collected light has traversed the background medium, and thus the measured absorption coefficient starts to shift toward the absorption coefficient of the background medium. This shift is exaggerated in darker heterogeneities because of the large difference between the optical properties of the heterogeneity and of the background. In the smaller heterogeneities the photons collected by the smaller SDS have traveled a higher percentage of their flight through the heterogeneity than the photons collected

at the longer SDS. In summary, a measurement accuracy of at least 70% was achievable for heterogeneities with a radius comparable to the large SDS, and there is clearly a measurable difference between the background and the heterogeneities with a radius as small as 2.5 mm.

There are several refinements that should improve the accuracy of the PMS probe. Adding a light baffle to the probe to limit the amount of light leaking between the source and the detector fibers may prevent the roll-off in optical properties that is seen with the darker phantoms. Simulations have shown that photons travel a more coherent path at higher modulation frequencies.⁸ Thus increasing the modulation frequencies may improve the measurement accuracy of smaller-sized heterogeneities. Additionally, changing the modulation frequency may enable the mean penetration depth for a fixed SDS to be varied.

In conclusion, we have constructed a novel PMS probe that will fit inside the bore of a Mammatome breast biopsy needle. This probe has been demonstrated to measure the optical properties of both homogenous and heterogeneous phantoms that are representative of human breast tissue. Probes of a similar design could be inserted into the body through an endoscope or a catheter, thus enabling the diagnostic capabilities of PMS measurements to be used on parts of the body that are not accessible with transcutaneous PMS methods.

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